The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers

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The effects of the acute administration of nicotine [through nicotine inhalers (NI) and placebo inhalers (PI)], nicotine-containing tobacco (NT), and denicotinized tobacco (DT), on smokers' subjective responses and motivation to smoke were examined in 22 smokers (12 male, 10 female; 11 low dependent, 11 high dependent). During four randomized blinded sessions, participants self-administered NI, PI, NT, or DT, and assessed their effects using Visual Analogue Scales and the Brief Questionnaire of Smoking Urges. They could then self-administer their preferred brand of cigarettes using a progressive ratio task. NT and DT were each associated with increased satisfaction and relaxation as well as decreased craving relative to the inhalers and NT increased ratings of stimulation relative to each of the other products. Both NT and DT delayed the onset of preferred tobacco self-administration relative to NI and PI but only NT reduced the total amount self-administered. Sex differences were evident in the effects of DT on withdrawal-related cravings with women experiencing greater DT-induced craving relief than men. Findings suggest that DT is effective in acutely reducing many smoking abstinence symptoms, especially in women, but a combination of nicotine and non-nicotine tobacco ingredients may be necessary to suppress smoking behavior. *Behavioural Pharmacology* **00:000–000 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Despite decreases in smoking rates over the past two decades, tobacco use remains prevalent and pervasive (World Health Organization, 2008). Although a majority of smokers report that they intend to quit within 6 months, most quit attempts fail (e.g. Hughes *et al.*, 2004; Brown *et al.*, 2005), even when assistance is sought and current best practice treatments are used (Cook *et al.*, 1995; Hughes *et al.*, 2003). Many tobacco cessation programs routinely use nicotine replacement therapies (NRTs) as a primary means of aiding cessation. The use of NRTs has been shown to increase overall quit rates but in the majority of cases NRTs do not prevent relapse to smoking (e.g. Hughes *et al.*, 2003) and many smokers seem to be resistant to NRT-based treatments even when repeated NRT-assisted quit attempts are made (Fagerstrom, 1999; Hughes *et al.*, 2000). Individual differences in smoking cessation outcomes using NRTs seem to be in part mediated by the degree to which NRTs are able to suppress cigarette craving and other tobacco abstinence symptoms (e.g. Evans *et al.*, 2006). NRT-induced suppression of abstinence symptoms is well established (e.g. Hughes *et al.*, 2003; Evans *et al.*, 2006) but smokers are highly heterogeneous (e.g. Piasecki *et al.*, 2003; Furberg *et al.*, 2005) and individual differences have been documented in the degree of subjective craving and withdrawal symptom relief provided by NRTs (e.g. Killen *et al.*, 1990; Wetter *et al.*, 1999). Such findings suggest that non-nicotine factors may be important for the maintenance of tobacco addiction in many smokers.

Although the addictive properties of tobacco are often attributed exclusively to nicotine (e.g. US Department of Health and Human Services, 1988), the reinforcing effects of nicotine in the absence of tobacco have not been conclusively shown using adequately blinded protocols (Dar and Frenk, 2004; Fulton and Barrett, 2008). Moreover, tobacco smoke contains several thousand compounds in addition to nicotine (Hoffmann and Hoffmann, 1998), and many of these might contribute to tobacco's addictive properties either independently (Rodd-Henricks *et al.*, 2002) or in combination with nicotine (e.g. Talhout *et al.*, 2007; Villegier *et al.*, 2007). To date, little research focus has been directed toward examining the role of non-nicotine tobacco ingredients for the addictive properties of tobacco. However, growing evidence suggests that the replacement of non-nicotine smoking-related stimuli through denicotinized tobacco (DT) may relieve many symptoms of craving and smoking withdrawal at least in some smokers. DTs have been found to provide a significant degree of subjective satisfaction and immediate craving reduction (Baldinger *et al.*, 1995; Butschky *et al.*, 1995; Westman *et al.*, 1996; Gross *et al.*, 1997; Pickworth *et al.*, 1999; Rose *et al.*, 2000;

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Buchhalter *et al.*, 2001; Donny *et al.*, 2007) but, as with NRTs, there seems to be considerable variability in responses to DT (e.g. Finnegan *et al.*, 1945; Brauer *et al.*, 2001; Barrett *et al.*, 2006) and smokers seem to vary in the degree to which they miss the nicotine (e.g. Finnegan *et al.*, 1945).

A number of individual difference variables seem to have some utility for predicting the response to NRTs (e.g. Yudkin *et al.*, 1996; D'Angelo *et al.*, 2001) and/or non-nicotine smoking stimuli (e.g. Brauer *et al.*, 2001; Rose, 2006). For example, while male sex (D'Angelo *et al.*, 2001) and low levels of tobacco dependence (Yudkin *et al.*, 1996) tend to predict more favorable treatment outcomes with NRTs, female sex (Rose, 2006) and high levels of tobacco dependence (Brauer *et al.*, 2001) seem to be associated with more positive responses to the administration of non-nicotine smoking stimuli. Although the extent to which these aggregate results have clinical implications for the individual smokers remains unknown, such findings are consistent with the notion that there may be individual differences in the relative roles of nicotine and non-nicotine tobacco constituents for the maintenance of smoking behavior.

To begin to clarify the relative importance of nicotine and non-nicotine tobacco constituents for tobacco use in different smokers, this study examined the acute subjective effects of nicotine in the absence of tobacco [through nicotine inhalers (NI) and placebo inhalers (PI)], tobacco in the absence of nicotine (through DT), and nicotine-containing tobacco (NT), and their effects on subsequent smoking behavior in a heterogeneous sample of adult smokers.

Methods

Participants

Nontreatment-seeking male and female smokers were recruited from the Halifax Nova Scotia community. Participants were recruited on the basis of either being highly dependent on tobacco [Fagerström Test for Nicotine Dependence (FTND) ≥ 5] or having very low levels of tobacco dependence (FTND ≤ 2). Potential participants were told that the study would involve four experimental test sessions, plus one nonexperimental session to complete screening measures and to provide a nonabstinent carbon monoxide (CO) breath sample, and all were informed that they would be required to remain abstinent from all illicit and prescription drugs for the duration of the study. A total of 26 individuals were invited to participate in the study. All of the participants were medically healthy, free from current or previous mental illness including past or present substance use disorders (excluding nicotine dependence), all had reached the minimum age to legally consume tobacco in Canada and none intended to quit smoking over the subsequent 6 months. The study was carried out in accordance with the Declaration of Helsinki and all participants provided written informed consent.

Tobacco

Two types of tobacco that differ in nicotine content (nicotine-containing Quest 1, Vector Tobacco; and denicotinized Quest 3, Vector Tobacco, Mebane, North Carolina, USA) were used in the experiments. The manufacturer-reported maximum nicotine yield of the DT was 0.05 mg while the NT had an average reported yield of 0.6 mg. Both types of tobacco had reported tar yields of 10 mg.

Inhalers

In sessions using an acute nicotine challenge, a NI (10 mg; 4 mg deliverable, Pharmacia, Mississauga, Ontario Canada) was used. Nicotine administration through an inhaler was selected owing to its tolerability relative to other forms of nicotine administration (Schneider *et al.*, 2004) and to inhalers' similarity to cigarettes across several sensory motor and administration parameters. In the placebo condition, an inhaler identical in appearance but containing a pharmacologically inert solution was used, and the inhalation regimen was identical to that of the nicotine condition.

Blinding

The NT and NI were prepared to appear identical to the DT and PI, respectively, and both the experimenter administering the session and the participant were blinded to their contents. To minimize demand characteristics associated with having a priori knowledge of the possible test conditions (Fulton and Barrett, 2008), participants were informed that the inhalers and tobacco could vary in some ingredients, but not that they would vary in their nicotine contents specifically.

Carbon monoxide measurement

To verify tobacco abstinence, a breath CO analyzer (Vitalograph, Lenexa, Kansas, USA) was used. This instrument enables a quantification of CO exposure ranging from 0 to 500 parts per million and CO measurement is considered to be a valid and reliable index of degree of recent tobacco smoke exposure (SRNT Subcommittee on Biochemical Verification, 2002).

Subjective measures

The following subjective measures were administered at baseline and following the mandatory tobacco/inhaler administration.

Visual Analogue Scale (VAS)

The VAS consisted of 14 subjective mood descriptors (relaxed, satisfied, pleasant, anxious, stimulated, high,

sedated, jittery, alert, frustrated, dizzy, trouble concentrating, irritable, and head rush). Each item was rated on a 10 cm horizontal line labeled with the integers 1–10 and anchored with the endpoints 'Not at all' and 'Extremely'. Similar scales have been widely used to collect information about subjective drug effects in humans and this method of data collection has been shown to be reliable, valid, and sensitive to participants' subjective experiences (Bond and Ladder, 1972).

The Questionnaire of Smoking Urges-Brief version

The QSU-B is a 10-item, psychometrically sound self-report measure that assesses cravings across two dimensions (factor 1: intention to smoke; factor 2: withdrawal/negative affect relief). The QSU-B has been shown to be sensitive for measuring nicotine, tobacco and abstinence-related effects (Toll *et al.*, 2006).

Design

The research protocol comprised four experimental test sessions. All sessions were conducted between 09:00 and 16:00 h, a minimum of 2 and a maximum of 14 days apart, were double blind, and given in a randomized order. Participants arrived for each testing session having abstained from cigarettes for a minimum of 12 h, alcohol for a minimum of 24 h, and food and caffeine for a minimum of 4 h (caffeine-free fluid intake was not restricted before the sessions). Abstinence from tobacco was confirmed with a breath CO analyzer, using a maximum cutoff of 15 parts per million and a 50% minimum reduction relative to their nonabstinent breath sample. After completing baseline measures, participants were comfortably seated in a chair in front of a computer. They were then required to administer either an inhaler or two cigarettes over a 20-min period. During inhaler sessions participants were instructed to take one deep inhalation every 10 s throughout the entire administration period. This inhalation regimen was selected to ensure significantly elevated plasma nicotine concentrations at the time of the subjective and behavioral assessments (Schneider *et al.*, 2001). In the cigarette conditions participants were instructed to inhale the smoke and to complete the cigarette to the filter but the pace and duration of the 'puffs' were self-determined by the participants. Participants were given their first cigarette at the beginning of the administration period and second cigarette 10 min later. Following the tobacco/inhaler challenge participants completed a second subjective assessment (VAS, QSU-B) and provided another breath sample. They could then begin using a computerized progressive ratio (PR) task to earn puffs of their preferred brand of tobacco. For each puff participants were required to repeatedly press keys on a keyboard a predetermined number of times. The first puff required 10 key presses and for each subsequent puff the number of required key presses increased by one-and-a-third times (i.e. 13, 17, 22, etc.). Similar PR tasks have been shown to be sensitive to pharmacological manipulations (Barrett *et al.*, 2006, 2008) as well as to changes in mood and craving (Willner *et al.*, 2005; Willner and Jones, 2006).

Analyses

All data were analyzed using SPSS Version 15 (Chicago, Illinois, USA). The main behavioral outcomes were the number of button presses during the PR task to earn tobacco puffs during each session and the latency (time in seconds) to initiate this task. Because these data appeared skewed, they were screened for normality using the Kolmogorov–Smirnov method and it was determined that logarithmic transformations were necessary for each variable to satisfy the normality assumption. All data were analyzed using mixed modeling with challenge condition (NT, DT, NI, PI) entered as a fixed and repeated factor, sex, and dependence levels (FNTD ≤ 2 vs. FTND ≥ 5) as fixed factors and subject as a random factor. Covariance structure was selected on the basis of model simplicity and use of the likelihood ratio test (SPSS, 2002). For the VAS and QSU-B data, time (pre-challenge vs. postchallenge) was entered into the model as a fixed and repeated factor and the outcomes of interest were interactions of time with condition, sex, and/or dependence.

For all analyses, tests of simple main effects were conducted on the linearly independent pairwise comparisons among the estimated marginal means. For interactions, the simple effects of variables within each level combination of the other variable(s) were tested. To account for multiple testing, the threshold for statistical significance for all main effects and interactions was set at $P \leq 0.01$.

Results

Participants

Twenty-two participants (12 male, 10 female; 11 high dependence, 11 low dependence) enrolled in the study; 20 completed all four experimental sessions, one completed three sessions (NT, DT, NI) but withdrew owing to experiencing a trauma unrelated to the study, and one completed only two sessions (NI, PI) before relocating to another city. Because mixed models accommodate for missing data by simultaneously considering individual and group effects, the data from all 22 participants were retained for the analyses (post-hoc analyses revealed that the direction and nature of all main effects and interactions were the same when the sample was restricted to those completing all four experimental sessions). An additional four participants (one male, three females) were invited to participate after screening but did not complete any experimental sessions. Characteristics of participants included in the final analyses are presented in Table 1.

Table 1 Demographic and tobacco-use characteristics

	Age, mean (SD)	FTND score, mean (SD)	Cigarettes per day, mean (SD)	Nonabstinent CO (ppm), mean (SD)
Overall ($N=22$)	26.8 (9.0)	3.6 (2.9)	11.9 (9.3)	17.5 (10.8)
Male ($n=12$) 5 low FTND	27.0 (6.4)	3.7 (2.6)	11.3 (5.2)	17.5 (11.1)
Female ($n=10$) 6 low FTND	26.6 (11.0)	3.4 (3.3)	12.7 (13.0)	17.5 (11.0)
High FTND ($n=11$) 7 male	31.5 (10.5)	6.2 (1.3)	17.6 (10.3)	25.5 (9.2)
Low FTND ($n=11$) 5 Male	22.2 (2.8)	0.9 (0.8)	6.2 (2.0)	9.5 (4.7)

CO, carbon monoxide; FTND, Fagerström Test for Nicotine Dependence; SD, standard deviation.

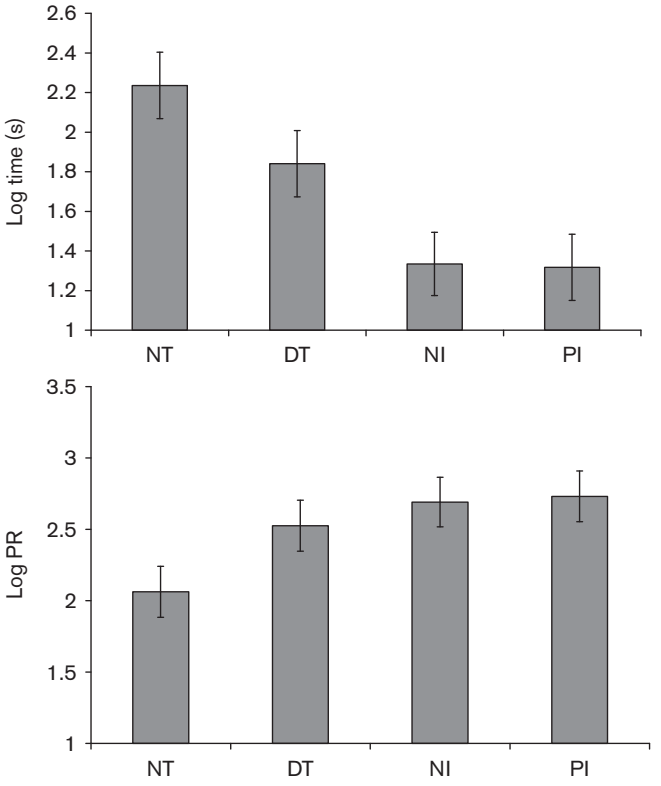
Self-administration

Two self-administration variables were assessed: the log PR values to earn preferred cigarette puffs and the latency (log time in seconds) to earn the first puff. There was a significant main effect of condition on latency to self-administration, [$F(3,49.0) = 7.1$, $P < 0.001$], reflecting a delay in the onset of self-administration in the NT and DT conditions relative to the NI and PI conditions (Ps < 0.01) (Fig. 1; upper). Analyses also revealed a significant main effect of condition on log PR values for cigarette puffs earned, [$F(3,52.0) = 6.7$, $P < 0.01$], reflecting significantly less self administration in the NT condition, relative to the DT, NI, or PI conditions (Ps < 0.01) (Fig. 1; lower). Self administration PR values did not reliably vary between DT, NI, and PI. There were no significant main effects or interactions involving sex or level of dependence for any of the self-administration variables.

Craving

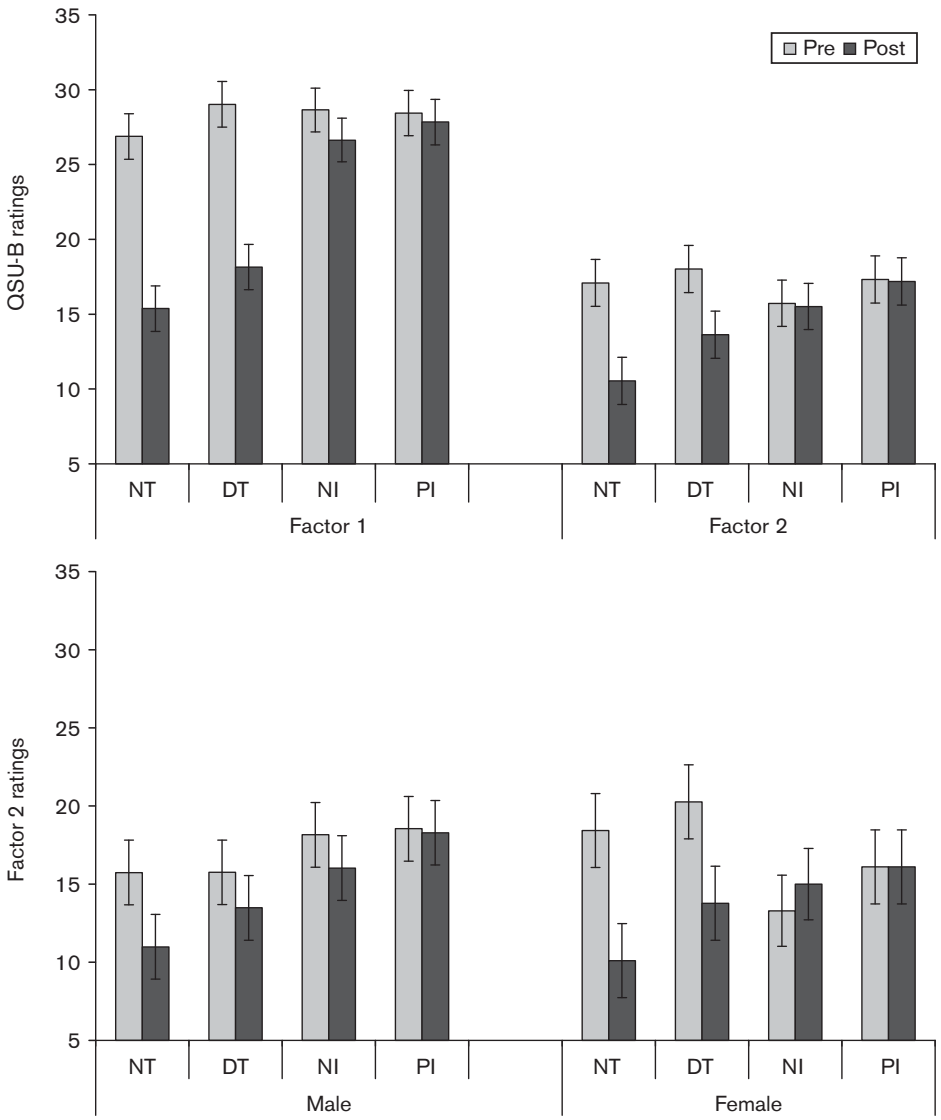
Two craving-related variables were assessed using the QSU-B: intention to smoke and withdrawal/negative affect relief. There was a significant condition × time interaction on factor 1 craving (intention to smoke), [$F(6,120.8) = 13.9$, $P < 0.01$], reflecting significantly decreased craving after NT and DT administration relative to the administration of NI and PI (Ps < 0.01). There was also a significant condition × time interaction on factor 2 craving (withdrawal/negative affect relief), [$F(6,120.5) = 5.3$, $P < 0.01$], reflecting decreased postchallenge craving in the NT condition relative to the NI and PI conditions ($P < 0.01$), as well as decreased craving in the DT condition relative to PI ($P < 0.01$) (Fig. 2; upper). Analyses also revealed a significant sex × condition × time interaction, [$F(6,120.5) = 3.0$, $P < 0.01$] (Fig. 2; lower). However, because there was significant variability in female prechallenge scores ($P < 0.01$), a post-hoc analysis was conducted to examine a potential sex × condition interaction in postchallenge scores when using prechallenge scores as a repeated measures covariate. Again, the analysis revealed a significant condition × sex interaction [$F(7,52.4) = 6.4$, $P < 0.01$]. Among women there was a significant main effect of condition [$F(3,60.4) = 11.4$, $P < 0.001$], reflecting decreased withdrawal-related craving after the administration of either NT or DT relative to NI and PI (Ps < 0.001). In men condition differences were evident only at a trend level, [$F(3,57.8) = 2.9$, $P = 0.04$] with decreased withdrawal-related craving after NT relative to PI only ($P < 0.01$) and no differences between any of the other conditions ($P > 0.1$). Moreover DT tended to decrease factor 2 craving in women relative to men [$F(1,74.0) = 4.9$, $P = 0.03$] and no other postchallenge sex differences were evident (Ps > 0.1).

Fig. 1



Mean (± SE) latency to self-administer preferred tobacco in log transformed seconds for each experimental session (upper). There was a significant delay in self-administration after the nicotine-containing tobacco (NT) and denicotinized tobacco (DT) challenges relative to each of the inhaler challenges. Mean (± SE) log transformed progressive ratio (PR) values for each experimental condition (lower). Participants earned significantly fewer preferred tobacco puffs after the NT challenge relative to each of the other conditions. NI, nicotine inhalers; PI, placebo inhalers.

Fig. 2

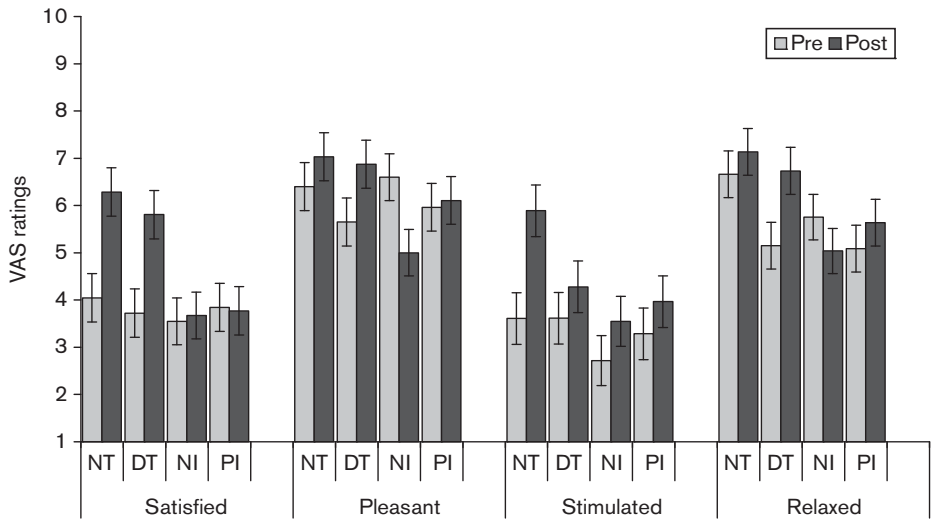


Mean (±SE) factor 1 and factor 2 Questionnaire of Smoking Urges-Brief (QSU-B) subscores before and after each experimental challenge (upper). Administration of both nicotine-containing tobacco (NT) and denicotinized tobacco (DT) significantly reduced factor 1 craving relative to each of the inhaler challenges while NT significantly reduced factor 2 craving relative to each of the other conditions and DT reduced it relative to each of the inhalers. A sex × condition × time interaction revealed that administration of DT reduced factor 2 craving relative to nicotine inhalers (NI) and placebo inhalers (PI) in women but not in men (lower).

Mood

There was a significant interaction of condition × time on ratings of 'satisfied' [$F(6,121.3) = 5.3$, $P < 0.001$], reflecting greater satisfaction after the administration of NT and DT relative to either of the inhaler conditions (Ps < 0.001). There was also a significant condition × time interaction on ratings of 'pleasant' [$F(6,120.4) = 4.8$, $P < 0.01$], with participants rating NI as being less pleasant than each of the other products (Ps ≤ 0.01), as well a significant condition × time interaction on ratings of 'stimulated' [$F(6,121.0) = 4.8$, $P < 0.01$], with participants reporting greater stimulation after NT relative to DT, NI, and PI (Ps ≤ 0.01) (Fig. 3). Analyses also revealed a significant condition × time interaction on ratings of 'relaxed' [$F(6,120.9) = 5.7$, $P < 0.01$] but because prechallenge differences in ratings of relaxed were evident [$F(3,121.0) = 4.1$, $P < 0.01$], a post-hoc analysis was conducted to determine whether there were postchallenge differences between the conditions when considering prechallenge scores as a covariate. There was a significant effect of condition on postchallenge ratings [$F(3,56.4) = 7.7$, $P < 0.001$], with the administration of either NT or DT being associated with significantly greater relaxation than the administration of NI (Ps < 0.001).

Fig. 3



Mean (± SE) ratings of 'satisfied', 'pleasant', 'stimulated' and 'relaxed' before and after each experimental challenge. Nicotine-containing tobacco (NT) and denicotinized tobacco (DT) were rated as more satisfying than each of the inhalers; nicotine inhalers (NI) as being less pleasant than each of the other products, NT as producing more stimulation than each of the other products, and ratings of 'relaxed' were significantly greater after NT and DT administration relative to NI administration. PI, placebo inhalers; VAS, Visual Analog Scale.

There were no other significant main effects or interactions involving condition for any of the remaining variables. There were, however, significant sex × dependence × time interactions for ratings of 'sedated' $F(2,31.0) = 5.3$, 'irritable' $F(2,31.0) = 7.0$, and 'head rush' $F(2,28.7) = 7.9$ ($P < 0.01$) with greater increases in ratings in high dependence women and low dependence men, relative to other participants, for both 'irritable' and 'head rush', as well as in low dependence males for 'sedated' ($P < 0.01$). There was also a significant sex × time interaction for ratings of 'dizzy' [$F(2,30.3) = 6.9$, $P < 0.01$], reflecting relatively increased post-challenge dizziness in men.

Discussion

The present results suggest that non-nicotine tobacco smoking factors may significantly contribute to the addictive properties of smoking. Across smokers, DT was found to significantly increase subjective satisfaction and reduce intentions to smoke as well as to delay the onset of preferred tobacco self-administration, and among women DT also significantly reduced withdrawal-related craving. Interestingly, in addition to its effects on craving and tobacco use, DT was found to be associated with increased feelings of relaxation across smokers relative to NI (Fig. 3). These findings raise the possibility that non-nicotine tobacco smoking factors may be especially important for the calming effects of tobacco smoking; effects that are often considered paradoxical in light of the stimulant properties of nicotine (Nesbitt, 1973). Collectively these results suggest that, for many smokers, targeting non-nicotine smoking factors may be an effective means of reducing abstinence symptoms as well as suppressing preferred tobacco use. It should be noted, however, that NT was found to reduce preferred tobacco self-administration as well as produce greater subjective stimulation relative to DT. Such findings suggest that a combination of nicotine and non-nicotine smoking factors may be important to the reinforcing value of cigarettes.

Although this study did not assess the mechanisms by which DT suppressed tobacco craving and use, or increased subjective reports of relaxation and satisfaction, it is possible that non-nicotine tobacco constituents contributed to these effects through a neuropharmacological action. A number of ingredients found in tobacco smoke, apart from nicotine, are known to have central actions and to interact with mechanisms that mediate reinforcement (e.g. Fowler *et al.*, 1996; Rodd-Henricks *et al.*, 2002; Talhout *et al.*, 2007; Villegier *et al.*, 2007; Clemens *et al.*, 2009). Despite this, the extent to which various non-nicotine tobacco constituents contribute to tobacco craving and withdrawal remains largely uninvestigated. Alternatively, it is possible that the sensory properties of DT, independent of any neuropharmacological effect, account for the observed effects. Attenuating smoking-related sensory cues has been associated with a reduction in smoking reinforcement (Perkins *et al.*, 2001; Rose *et al.*, 1984, 1985) and it is possible that the replacement of such sensory cues in the absence of any pharmacological action is sufficient to attenuate tobacco craving and smoking (Rose, 2006; Donny and Jones, 2009). However, it is important to note that in this study, the use of NI and PI would be expected to control for many of the sensory aspects of smoking (Schneider *et al.*, 2001).

DT was found to reduce withdrawal-related craving in women but not in men (Fig. 2; lower). It is possible that this sex difference may result from a differential involvement of nicotine and non-nicotine tobacco constituents in the addictive properties of tobacco in men and women. Nicotine-specific therapies seem to be more effective in promoting smoking cessation in men than in women (Perkins *et al.*, 1999) and although little is currently known about individual differences in response to pharmacological effects of non-nicotine tobacco constituents, evidence suggests that women may have a greater susceptibility to smoking-related expectancy effects than men (Perkins *et al.*, 2006). Irrespective of the mechanism, the ability of DT to attenuate tobacco withdrawal in women suggests that it may be important to target non-nicotine smoking factors for smoking cessation in many smokers. However, it is also important to note that across smokers only NT was effective in significantly reducing the total amount of preferred tobacco self administered. Thus, it may be appropriate to target a combination of nicotine and non-nicotine tobacco constituents to suppress tobacco use maximally in both men and women.

A relatively unexpected result of this study was an adverse response to NI, as reflected by significantly decreased ratings of 'pleasant'. Although in past research participants have shown a preference for NI relative to other forms of NRT (Schneider *et al.*, 2004), it is important to note that smokers often rate nicotine apart from tobacco as having unpleasant effects across modes of administration (e.g. Dar and Frenk, 2004; Rose, 2006), and in this study NI were compared with tobacco and with an inert placebo, not with other forms of nicotine. Moreover, in contrast to most other investigations, participants in this study were not informed that they would be receiving nicotine during one of the inhaler conditions. Earlier research suggests that the expectation that one is receiving nicotine increases the likeability and clinical efficacy of NRTs and that expectancies interact with pharmacological factors to produce overall subjective and behavioral responses (e.g. Hughes *et al.*, 1989; Perkins *et al.*, 2009). Thus, the nonpharmacological aspects of nicotine administration would be expected to be de-emphasized in this study and this may account for some of the effects (and lack thereof) associated with NI administration. It is also important to note that the experimental protocol required participants to administer 120 inhalations over 20 min during each of the inhaler conditions. Although this inhalation regimen was selected to ensure maximum nicotine concentrations at the time of the subjective and behavioral assessments, it is possible that it decreased the likeability of the NI. In past research, inhalation regimens requiring 50% fewer inhalations of NI over the same time period have been well tolerated (Schneider *et al.*, 2005) and resulted in plasma nicotine concentrations similar to those achieved by other NRTs (Schneider *et al.*, 2001). Although the present investigation required higher levels of NI intake to maximize nicotine exposure, participants readily accepted this dosing procedure and there was no evidence of toxicity or other adverse events.

The present results should be interpreted in light of the following methodological considerations. First, because the participants were not treatment-seeking and were not attempting to remain abstinent during the experimental sessions, it is not clear to what extent the findings can extend to those attempting to quit smoking. Although a number of recent trials have examined the use of DT as an adjunct to NRT for smoking cessation (Rezaishiraz *et al.*, 2007; Becker *et al.*, 2008), to my knowledge the acute effects of DT on tobacco reinforcement have not been examined in samples attempting to quit smoking. Additional research should be directed toward investigating non-nicotine smoking factors in those attempting to achieve abstinence. Second, the DT used in this study contains trace amounts of nicotine (Vector Tobacco), and as a result a potential nicotinic contribution to DT-related effects cannot be excluded. However, because the nicotine yield of the NT is approximately 12 times higher than that of the DT, and DT administration has been shown to result in substantially less nicotinic receptor occupancy than NT (Brody *et al.*, 2009), it is unlikely that similarities observed between NT and DT in this study can be solely attributed to their nicotinic effects. Third, although the sample size was well within the norms for assessing within-subjects drug effects, it may have been inadequate to detect certain interaction effects involving sex and/or dependence, and further study will be required to fully evaluate the effects of nicotine and non-nicotine smoking factors on tobacco craving and administration in different subsets of smokers. Finally, because NT and NI have different delivery kinetics, it is possible that pharmacokinetic differences between the products may account for some of the differences in their subjective and behavioral effects. Conclusive evidence linking the delivery kinetics of nicotine to tobacco reinforcement is currently lacking (Dar and Frenk, 2007), and evidence suggests that DT may be preferred to nicotine in the absence of tobacco, even when the delivery kinetics of nicotine are identical to those achieved by smoking (Rose, 2006). Moreover, explanations based on nicotine kinetics are unlikely to account for similarities observed between NT and DT. Nevertheless, it will be important to examine nicotine and non-nicotine smoking factors under a variety of conditions to understand more fully their relative contributions to tobacco addiction.

In conclusion, DT administration seems to provide significant subjective satisfaction as well as to reduce tobacco abstinence symptoms. Moreover, although NT was superior to DT in suppressing smoking behavior, the administration of NI tended to have little effect on

acute tobacco use relative to placebo. These findings suggest that non-nicotine smoking factors may be important to smoking-related reinforcement and may be an appropriate target for smoking cessation. Increased attention should be directed toward identifying the pharmacological and/or nonpharmacological elements of DT that are effective in suppressing tobacco craving and administration.

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